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EXAMINER	
MARVICH, MARIA	

ART UNIT	PAPER NUMBER
1636	16

DATE MAILED: 10/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/897,006	Applicant(s) BLECK, GREGORY T.	
	Examin r Maria B Marvich, PhD	Art Unit 1636	

-- Th MAILING DATE of this communication appears on th cover sh et with the corr spondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 July 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-25,28 and 33-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-25,28 and 33-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This office action is in response to an amendment filed 7/28/03. Claims 26, 27, 29 and 31-32 are cancelled, claim 21 is amended and claims 34-41 have been added. Claims 21-25, 28 and 33-41 are pending. Claims 1-20 and 30 have been withdrawn.

Claim Rejections - 35 USC § 102

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 21-24 are rejected under 35 U.S.C. 102(e) as being anticipated by Piechaczyk et al. (US application 2002/0168339). See entire document. **This rejection is maintained for reasons of record in the office action filed 4/23/03, Paper No. 14 and repeated below.**

Piechaczyk et al teach methods for the production of Tg10 antibody using pLXPXSN, a retroviral vector, in which the heavy and light chains of the immunoglobulin are expressed from either side of an IRES and this vector is called PM130 (see e.g. paragraph 0070). PM130 was used to express a functional Tg10 antibody (see e.g. table 1). Absent evidence to the contrary, the subunits are expressed in about a 0.9:1.1 ratio as equimolar ratios of the heavy and light chains are required for immunoglobulin assembly.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 21-25, 28 and 33-41 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. **This rejection is maintained for reasons of record in the office action filed 4/23/03, Paper No. 14 and repeated below. This rejection is extended to newly added claims 34-41.**

Applicant's claims read on a first and second exogenous gene that encodes a first and second immunoglobin chain. The claim therefore reads on a genus claim encompassing any immunoglobin gene from any species.

The written description requirement for a genus claim may be satisfied through sufficient description of a relevant a representative number of species by actual reduction to practice or by disclosure of relevant identifying characteristics such as structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure or by a combination of such identifying characteristics sufficient to show applicants were in possession of the claimed genus.

In the instant case, applicants teach the production of MN14, LL2, and botulinum toxin immunoglobin heavy and light chains. The genomic version of any of the recited genes is not disclosed by the specification nor does the prior art apparently disclose the entire gene. While the cDNAs may be known, not all of the genes have been characterized. Because all of the components of the gene such as regulation sequences, introns, and exons must be determined empirically in order to generate the immunoglobin genes, applicant claims the gene without any

disclosure about its structure. The skilled artisan would not conclude that applicant was in possession of viral vector comprising the claimed genes. **It would be remedial to recite first exogenous coding sequence and second exogenous coding sequence.**

Response to Arguments

Applicants traverse the claim rejections under 35 U.S.C. 102(e) as being anticipated by Piechaczyk et al on pages 9-10 of the amendment filed 7/28/03, Paper No. 15. Applicant argues that no extrinsic evidence is provided to establish that the heavy and light chains of TG10 antibody of Piechaczyk et al are expressed at about a 0.9:1.o ratio. It is said that the examiner appears to rely upon anticipation by inherency and possibilities, as this limitation is not necessarily present in the teachings of Piechaczyk et al. In contrast, applicants are said to have established that this reasoning is incorrect based upon page 31-33 of the instant specification. Pages 31-33 teach use of an IRES/signal peptide sequences to express two genes of interest in the same construct. The IRES sequence is used for expression of two genes from one construct and the signal peptide for secretion of the second protein. The second codon of the signal peptide is mutated from an ATG to a GCC changing the second amino acid of the α-lactalbumin signal peptide from a methionine to an alanine to facilitate more efficient translation initiated by the IRES. It is also contemplated that the second codon of the bovine α-S1 casein signal peptide is mutated from AAA to GCC. As incorrectly assembled immunoglobin molecules are possible following use of the expression vector of Piechaczyk et al, functional molecules do not necessarily mean that the heavy and light chains have been expressed at about a 0.9:1 ratio. Also, it is pointed out that Piechaczyk et al do not teach a vector comprising a signal sequence

operably linked to an IRES wherein the second codon of the signal sequence is GCC which limitations are recited in the newly added claims 34-41.

Applicant's arguments filed 7/23/03 have been fully considered but they are not persuasive. The invention recites a method for producing a first immunoglobin gene and a second immunoglobin gene separated by an internal ribosome entry site in a retroviral vector in which the first and second gene are expressed at a ratio of about 0.9:1.1 to 1:1. The expression of the two genes at this ratio occurs, according to an amendment filed 8/25/03 this is taught on page 31-33 of the specification, as "The IRES allows translation of the gene to start at the IRES sequence, thereby resulting in the expression of two genes of interest in the same construct". It is further explained in the specification that in preferred embodiments, heavy and light chains are expressed in a variety of ratios, the majority of the heavy and light chains are correctly assembled in a ratio of 1:1 to form a functional (e.g. able to bind an antigen) antibody (page 45, lines 11-19). Absent evidence to the contrary, no special steps are provided for the preferred ratios. Rather, an IRES sequence is used to express a single transcript from which both immunoglobin coding sequences are translated. The resultant ratio appears to be an inherent result of the design of a vector comprised of a heavy and light immunoglobin chain separated by the IRES, a fact which is suggested by the experimental disclosure of the instant invention as illustrated in examples 1 and 6-16. Examples 1 and 6-16 detail preferred constructs and expression of immunoglobin genes from these constructs. For purposes of identifying prior art, conditions that are depicted in these examples are assumed to be adequate to perform the instant invention. In example 1, the IRES sequence comes from pLXIN, a retroviral vector with an IRES sequence, and use of this expression vector is shown in example 6 and 8 for example to

generate a ratio of heavy and light chains of 1:1. The invention of Piechaczyk et al. utilizes pLXPXSN, a retroviral vector with an IRES sequence page 4-5, paragraph 0070. Similar to the instant invention, the IRES sequence of pLXPXSN separates the coding sequence of a heavy and light chain of an immunoglobin. Similar to the instant invention, Piechaczyk et al teach expression of heavy and light chains from their retroviral vector encoding these chains. Absent evidence to the contrary, the experimental conditions of the instant invention do not differ from the experimental conditions taught by Piechaczyk et al.

The prior art teaches that IRES sequences in bicistronic vectors lead to expression of genes prior to and following the IRES in about generally equimolar ratios, which reflects a 1:1 or a ratio of about 0.9:1.1. For example, see US 6,479,284 and 5,665,567. US 6,479,284 teaches use of a vector for expression of stoichiometric units of light and heavy immunoglobin chains which stoichiometry is 1:1. US 5,665,567 teaches use of an expression vector with an IRES for equimolar expression of A and B polypeptides. Therefore, and not based upon possibilities, it is inherent in the vectors of Piechaczyk et al that the heavy and light chains are expressed in a ration of about 0.9:1.1 to 1:1 ratio.

Applicants traverse the claim rejections under 35 USC 112, first paragraph, written description on pages 11-14 of the amendment filed 7/28/03, Paper No. 15. Applicants argue that the position taken by the examiner is contrary to the Written Description Guidelines specifically as detailed in Example 18 of the Guidelines. As in example 18, the invention recites **use** of composition in a process and not the composition itself. Therefore, the focus on the immunoglobin coding sequence is misplaced. Furthermore, applicants point to the specification at page 7 which defines "gene" as a nucleic acid that comprises coding sequence necessary for

the production of a polypeptide or precursor and teaches that the term also encompasses the coding region of a structural gene and includes sequence located adjacent to the coding region as well as cDNA and genomic versions of a gene. Applicants state that sufficient immunoglobin coding sequences have been provided and multiple gratuitous examples of additional coding sequences are not required, as the inventors are not required to describe in detail what is known in the art.

Applicant's arguments filed 7/23/03 have been fully considered but they are not persuasive. While the invention recites a process that uses immunoglobin genes and not the actual immunoglobin genes, absent a clear disclosure of the elements of the process, the invention cannot be made and used. The elements of exogenous genes encoding immunoglobin are unclear and therefore, the applicants have not met the requirements of 35 USC 112, first paragraph. While the applicant's invention recites a process for the production of immunoglobin, it does recite that immunoglobin genes are used in the invention. The genomic version of any of the recited genes is not disclosed by the specification nor does the prior art apparently disclose the entire gene. While it is understood that genes comprise coding sequences they also comprise regulation sequences, introns, and exons. The coding sequences for a variety of immunoglobin genes are known in the art. However, the genes encompassing these coding sequences are not well defined in the art. Therefore, it is recommended that the claim recite immunoglobin coding sequences rather than genes. Note that no indication has been given that multiple examples of known sequence are required in the application.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B Marvich, PhD whose telephone number is (703) 605-1207. The examiner can normally be reached on M-F (6:30-3:00). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD can be reached on (703) 305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 305-4242 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 305-3291.

Maria B Marvich, PhD
Examiner
Art Unit 1636

October 17, 2003

GERRY LEFFERS
PRIMARY EXAMINER